a hydrogen atom,

a loweralkyl group,

a phenyl group,

an aryl(loweralkyl) group;

or R^6 and R^4 and the atoms to which they are attached are taken together form a 5- to 7-membered ring containing one oxygen atom;

or R^6 and R^5 and the atoms to which they are attached are taken together form a 5- to 7-membered cycloalkyl group;

with the requirement that only one pair of substituents (R^4 and R^5), (R^4 and R^6) or (R^5 and R^6) may be taken together with the atoms to which they are attached to form a ring as defined above;

with a methylating agent in the presence of both a strong alkali metal base and a weak organic amine base in polar aprotic solvent or a mixture of polar aprotic solvents maintained at a reaction temperature for a period of time sufficient to complete the methylation, by adding the weak organic base prior to the addition of the methylating agent and the strong alkali metal base; and

(b) deprotecting at the 2' and/or 4" positions, and optionally deprotecting at the 9 position.

REMARKS

Claims 1-14 are pending. Previously-presented claim 8 has been amended. Support for this amendment is provided in column 1, lines 54-58 ("optionally protect the 9-oxo group" and "deprotect at the 2', 4" and 9-positions"). No new matter is introduced by this amendment.

Applicants submit that the newly-presented claims are narrower in scope than granted claims 1-7. Therefore, the claims presented here do not raise issues concerning enlargement of the scope of the claims under 35 U.S.C. § 251, final paragraph.

The examiner rejected claims 1-14 as being broadened in a reissue application filed outside the two-year statutory period. Similarly, the examiner rejected the claims because the reissue oath is defective if they present a broadening reissue. Applicants respectfully traverse these rejections. The examiner appears to have relied upon reasoning that appears in prior M.P.E.P. § 1412.03, pp. 1400-17, under "Broadening-Indirect Infringement" (8th edition, August 2001), for rejecting the claims as broadening. The Patent and Trademark Office no longer accepts this interpretation of 35 U.S.C. § 251, and has deleted this language from the current version of the M.P.E.P.

The current version of M.P.E.P. § 1412.03 (8th ed., revision 2, May 2004) is attached as Ex. A. The current version deleted the entire section entitled "Broadening-Indirect Infringement." Two "*" now appear on page 1400-23 where the prior language once appeared, to indicate that this language has been deleted. See M.P.E.P. § 1412.03 (8th ed., revision 2, May 2004) page 1400-23 (right column, above the title "Scope of Dependent Claim Not Enlarged). Attached as Ex. B is M.P.E.P. § 1412.03 (8th ed., August 2001) containing the prior language of now-superceded PTO interpretation.

Moreover, a new section has been added to M.P.E.P. § 1412.03 (8th ed., revision 2, May 2004) entitled "New Category of Invention Added in Reissue—Generally Not Broadening." Ex. A, page 1400-24. This section specifically authorizes the claim amendments presented here, and explains that under the current PTO interpretation, these claim amendments are not "broadening."

In particular, current M.P.E.P. § 1412.03 states that:

> (1) a process of using the product A (made by the process of the original patent) to make a product B, disclosed but not claimed in the original patent ...
>
> ...

is not broadening (i.e., this is not an enlargement of the scope of the original patent) because the 'newly claimed invention' contains all the limitations of the original patent claim(s).

Claims 8-14 take processes for producing A (protected 6-O-methylerythromycin derivatives) of the original patent claims and add processes for producing B (6-O-methylerythromycins), and these claimed processes were indisputably described in the original specification. See, e.g., column 1, lines 46-57, column 3, lines 37-40. New claims 8-14 fall squarely within the claims described in the section entitled "New Category of Invention Added in Reissue—Generally Not Broadening" and thus, are not broadening. Therefore, Applicants respectfully request that the learned Examiner withdraw her rejections on these grounds.

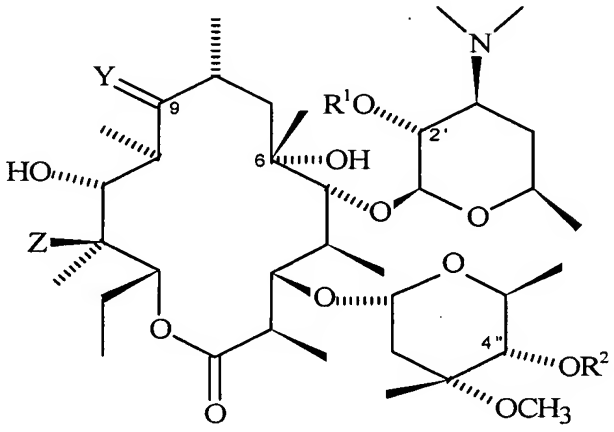
Claims 8-14 were rejected under 35 U.S.C. § 112, ¶ 2, as being indefinite. Although Applicants do not agree with the examiner's indefiniteness rejection, Applicants have amended claim 8 to clarify the subject matter which Applicants regard as the invention.

Deprotection at either the 2' or 4" positions, or at both the 2' and 4" positions, can be carried out on the starting material of claim 8. If a protected-9-oxime starting material is optionally selected from the Markush group of claim 8, deprotection at the 9-position can be carried out on the starting material of claim 8.

Applicants submit that pending claims 1-14 are allowable and request a timely issuance of a Notice of Allowance. Please feel free to call Stuart E. Pollack at (212) 336-2721 if the examiner has any questions regarding this application.

STATUS OF THE CLAIMS

1. (Previously presented) An improved process for selective alkylation of a hydroxy group at the 6-position of a compound of the formula:



wherein:

R^1 and R^2 are independently hydrogen or a hydroxy-protecting group, except that R^1 and R^2 may not both be hydrogen simultaneously; and

Y is selected from the group consisting of:

a) oxygen,

b) an oxime having the formula N-O-R^3, wherein R^3 is selected from the group consisting of:

hydrogen,

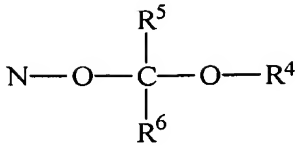
a loweralkenyl group,

an aryl(loweralkyl) group, or

a substituted aryl(loweralkyl) group;

and

c) an oxime having the formula:



wherein

R^4 is

a loweralkyl group,

a cycloalkyl group,

a phenyl group,

an aryl(loweralkyl) group,

or R^4 and R^5 or R^4 and R^6 and the atoms to which they are attached are taken together form a 5- to 7-membered ring containing one oxygen atom;

R^5 is

a loweralkyl group,

a loweralkoxymethyl group,

or R^5 and R^4 and the atoms to which they are attached are taken together form a 5- to 7-membered ring containing one oxygen atom,

or R^5 and R^6 and the atoms to which they are attached are taken together form a 5- to 7-membered cycloalkyl group;

and

R^6 is

a hydrogen atom,

a loweralkyl group,

a phenyl group,

an aryl(loweralkyl) group;

or R^6 and R^4 and the atoms to which they are attached are taken together form a 5- to 7-membered ring containing one oxygen atom;

or R^6 and R^5 and the atoms to which they are attached are taken together form a 5- to 7-membered cycloalkyl group;

with the requirement that only one pair of substituents (R^4 and R^5), (R^4 and R^6) or (R^5 and R^6) may be taken together with the atoms to which they are attached to form a ring as defined above;

Z is hydrogen, hydroxy or protected-hydroxy;

comprising reacting the compound with an alkylating agent in the presence of both a strong alkali metal base and a weak organic amine base in a polar aprotic solvent or a mixture of polar aprotic solvents maintained at a reaction temperature for a period of time sufficient to complete the alkylation, by adding the weak organic base prior to the addition of the alkylating agent and the strong alkali metal base.

2. (Previously presented) The process according to claim 1, wherein the weak organic amine base is selected from the group consisting of trimethyl-amine, triethylamine, tripropylamine, pyridine, 2-methoxypyridine, 1-methyl-pyrrolidine, 1-methylpiperidine, and 1-ethylpiperidine.

3. (Previously presented) The process according to claim 1, wherein the alkylating agent is selected from the group consisting of methyl bromide, methyl iodide, dimethyl sulfate and methyl-p-toluenesulfonate.

4. (Previously presented) The process according to claim 1, wherein the solvent is a mixture of solvents selected from the group consisting of N,N-dimethyl-formamide, dimethyl sulfoxide, N-methyl-2-pyrrolidone, hexamethylphosphoric triamide, tetrahydrofuran, 1,2-dimethoxyethane, acetonitrile and ethyl acetate.

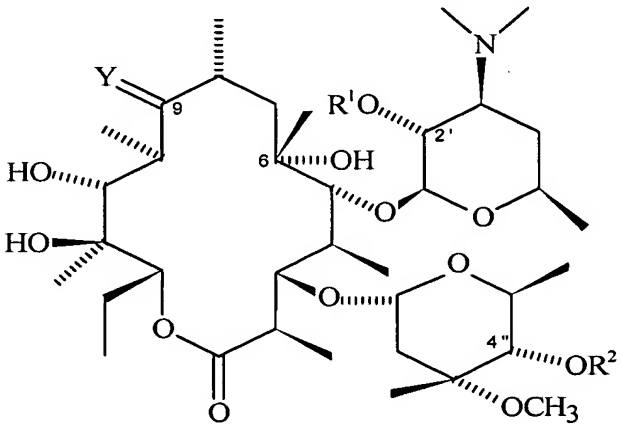
5. (Previously presented) The process according to claim 1, wherein R^1 and R^2 in the compound are independently hydrogen or a hydroxy-protecting group, which is benzyloxycarbonyl, acetyl, or a substituted silyl group of formula $SiR^7R^8R^9$, wherein R^7, R^8 and a R^9 are the same or different and each is a hydrogen atom, a loweralkyl group, a phenyl-substituted alkyl group in which the alkyl moiety has 1 to 3 carbon atoms, a phenyl group, a cycloalkyl group having 5 to 7 carbon atoms, or a loweralkenyl group having 2 to 5 carbon atoms; with the provisions that at least one of R^7, R^8 and R^9 is not a hydrogen atom.

6. (Previously presented) The process according to claim 1, wherein the compound is 2' mono trimethylsilyl erythromycin A oxime isopropyl cyclohexyl ketal, or 4" monotrimethylsilyl erythromycin A oxime isopropyl cyclohexyl ketal.

7. (Previously presented) The process according to claim 1, wherein the compound is a mixture of 2' mono trimethylsilyl erythromycin A oxime isopropyl cyclohexyl ketal and 4" monotrimethylsilyl erythromycin A oxime isopropyl cyclohexyl ketal.

8. (Amended) An improved process for preparing 6-O-methylerythromycin A comprising:

(a) reacting a compound of the formula



wherein:

R^1 and R^2 are independently hydrogen or a hydroxy-protecting group, except that R^1 and R^2 may not both be hydrogen simultaneously; and

Y is selected from the group consisting of:

a) oxygen,

b) an oxime having the formula N-O-R^3, wherein R^3 is selected from the group consisting of:

hydrogen,

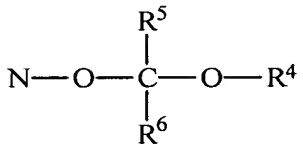
a loweralkenyl group,

an aryl(loweralkyl) group, or

a substituted aryl(loweralkyl) group;

and

c) an oxime having the formula:



wherein

R^4 is

a loweralkyl group,

a cycloalkyl group,

a phenyl group,

an aryl(loweralkyl) group,

or R^4 and R^5 or R^4 and R^6 and the atoms to which they are attached are taken together form a 5- to 7-membered ring containing one oxygen atom;

R^5 is

a loweralkyl group,

a loweralkoxymethyl group,

or R^5 and R^4 and the atoms to which they are attached are taken together form a 5- to 7-membered ring containing one oxygen atom,

or R^5 and R^6 and the atoms to which they are attached are taken together form a 5- to 7-membered cycloalkyl group;

and

R^6 is

a hydrogen atom,

a loweralkyl group,

a phenyl group,

an aryl(loweralkyl) group;

or R^6 and R^4 and the atoms to which they are attached are taken together form a 5- to 7-membered ring containing one oxygen atom;

or R^6 and R^5 and the atoms to which they are attached are taken together form a 5- to 7-membered cycloalkyl group;

with the requirement that only one pair of substituents (R^4 and R^5), (R^4 and R^6) or (R^5 and R^6) may be taken together with the atoms to which they are attached to form a ring as defined above;

with a methylating agent in the presence of both a strong alkali metal base and a weak organic amine base in polar aprotic solvent or a mixture of polar aprotic solvents maintained at a reaction temperature for a period of time sufficient to complete the methylation, by adding the weak organic base prior to the addition of the methylating agent and the strong alkali metal base; and

(b) deprotecting at the 2' and/or 4" positions, and optionally deprotecting at the 9 position.

9. (Previously presented) The process according to claim 8, wherein the weak organic amine base is selected from the group consisting of trimethylamine, triethylamine, tripropylamine, pyridine, 2-methoxypyridine, 1-methyl-pyrrolidine, 1-methylpiperidine, and 1-ethylpiperidine.

10. (Previously presented) The process according to claim 8, wherein the methylating agent is selected from the group consisting of methyl bromide, methyl iodide, dimethyl sulfate and methyl-p-toluenesulfonate.

11. (Previously presented) The process according to claim 8, wherein the solvent is a mixture of solvents selected from the group consisting of N,N-dimethyl-formamide, dimethyl sulfoxide, N-methyl-2-pyrrolidone, hexamethylphosphoric triamide, tetrahydrofuran, 1,2-dimethoxyethane, acetonitrile and ethyl acetate.

12. (Previously presented) The process according to claim 8, wherein R^1 and R^2 in the compound are independently hydrogen or a hydroxy-protecting group, which is benzyloxycarbonyl, acetyl, or a substituted silyl group of formula $SiR^7R^8R^9$, wherein R^7, R^8 and R^9 are the same or different and each is a hydrogen atom, a loweralkyl group, a phenyl-substituted alkyl group in which the alkyl moiety has 1 to 3 carbon atoms, a phenyl group, a cycloalkyl group having 5 to 7 carbon atoms, or a loweralkenyl group having 2 to 5 carbon atoms; with the provision that at least one of R^7, R^8 and R^9 is not a hydrogen atom.

13. (Previously presented) The process according to claim 8, wherein the compound is 2' mono trimethylsilyl erythromycin A oxime isopropyl cyclohexyl ketal, or 4" monotrimethylsilyl erythromycin A oxime isopropyl cyclohexyl ketal.

14. (Previously presented) The process according to claim 8, wherein the compound is a mixture of 2' mono trimethylsilyl erythromycin A oxime isopropyl cyclohexyl ketal and 4" monotrimethylsilyl erythromycin A oxime isopropyl cyclohexyl ketal.

Respectfully submitted,

Dated: June 24, 2005

Stuart E. Pollack
Reg. No. 43,862
Correspondence Address:

Attention: IP Docketing
Patterson, Belknap, Webb & Tyler, LLP
1133 Avenue of the Americas
New York, New York 10036
(212)336-2000
(212)336-2222 fax
Customer No. 23723